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(54) **PROCESS FOR MANUFACTURING GLATIRAMER ACETATE PRODUCT**

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See application file for complete search history.

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(57) **ABSTRACT**

The patent provides a process of preparing a pharmaceutical preparation of glatiramer acetate and mannitol in a suitable container comprising the steps of:

(i) obtaining an aqueous pharmaceutical solution of glatiramer acetate and mannitol;

(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

This patent further provides an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol, wherein the aqueous pharmaceutical solution

a) has a viscosity in the range of 2.0-3.5 cPa; or

b) has an osmolality in the range of 275-325 mosmol/Kg.

This patent also provides a prefilled syringe, an automated injector and a method of treatment of a human patient.

35 Claims, 11 Drawing Sheets

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Defendants Dr. Reddy's Laboratories Ltd., Dr. Reddy's Laboratories Inc., Sandoz Inc., Momenta Pharmaceuticals Inc., Mylan Pharmaceuticals Inc., Mylan Inc., Synthon Pharmaceuticals Inc., Synthon B.V., Synthon S.R.O., Pfizer Inc., Amneal Pharmaceuticals LLC, and Amneal GMBH's Initial Joint Invalidity Contentions

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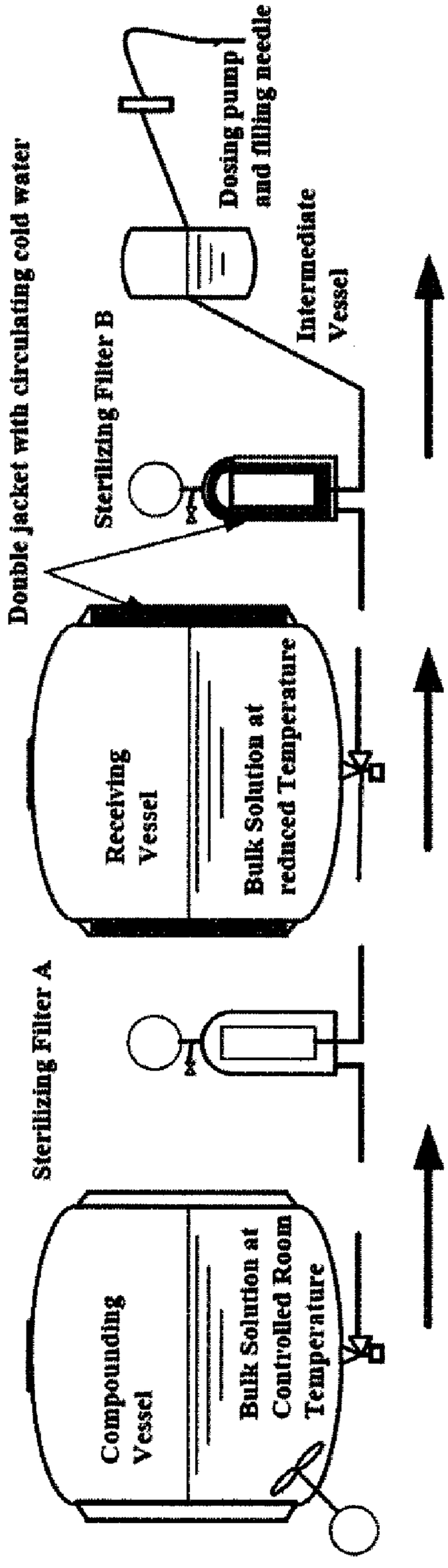
Compounding Vessel
Bulk Solution at Controlled Room Temperature
Sterilizing Filter A
Receiving Vessel
Bulk Solution at reduced Temperature
Double jacket with circulating cold water
Sterilizing Filter B
Dosing pump and filling needle
Intermediate Vessel

Figure 1

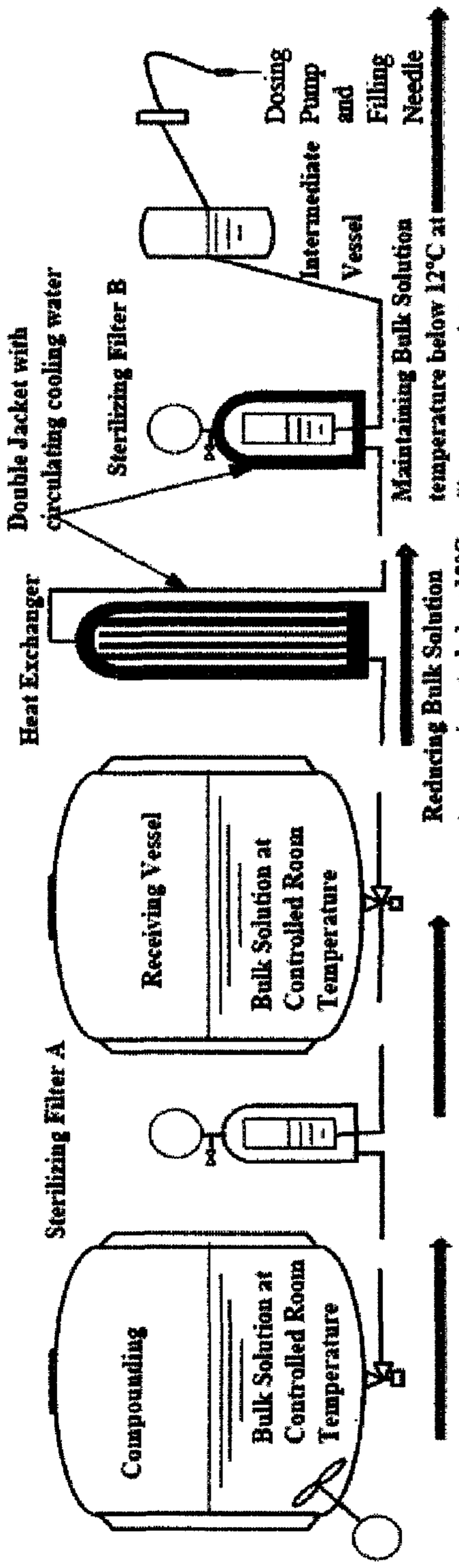
Sterilizing Filter A
Compounding
Bulk Solution at Controlled Room Temperature
Receiving Vessel
Heat Exchanger
Double Jacket with circulating cooling water
Sterilizing Filter B
Dosing Pump and Filling Needle
Intermediate Vessel
Reducing Bulk Solution temperature to below 12°C
Maintaining Bulk Solution temperature below 12°C at filter contact point

Figure 2

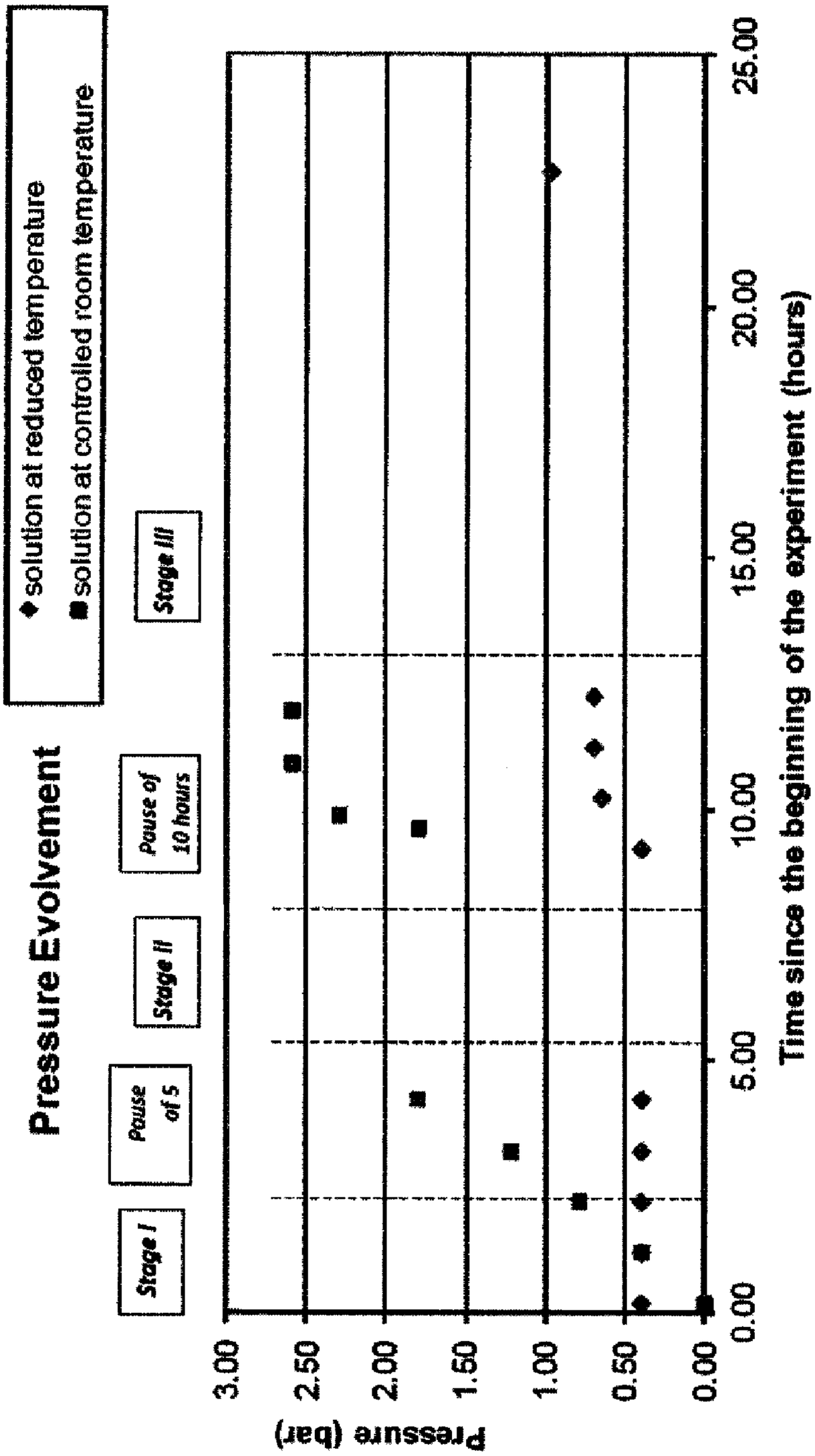
Pressure Evolvement
solution at reduced temperature
solution at controlled room temperature
Stage I
Pause of 5
Stage II
Pause of 10 hours
Stage III
Pressure (bar)
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Time since the beginning of the experiment (hours)
0.00
5.00
10.00
15.00
20.00
25.00

Figure 3

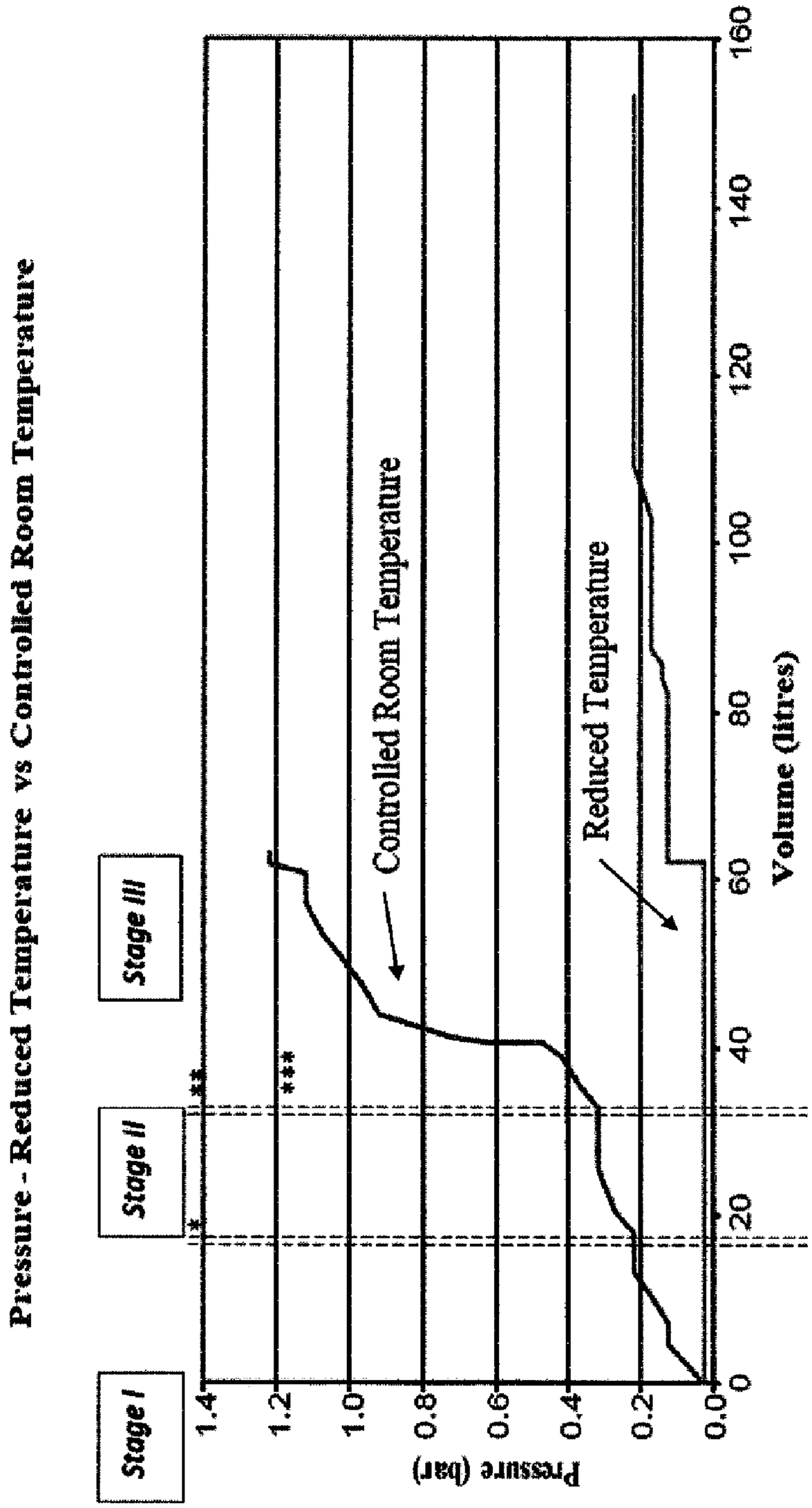
Pressure - Reduced Temperature vs Controlled Room Temperature
Stage I
Stage II
Stage III
*
**
***
Controlled Room Temperature
Reduced Temperature
Pressure (bar)
Volume (litres)
0,0
0,2
0,4
0,6
0,8
1,0
1,2
1,4
0
20
40
60
80
100
120
140
160

Figure 4

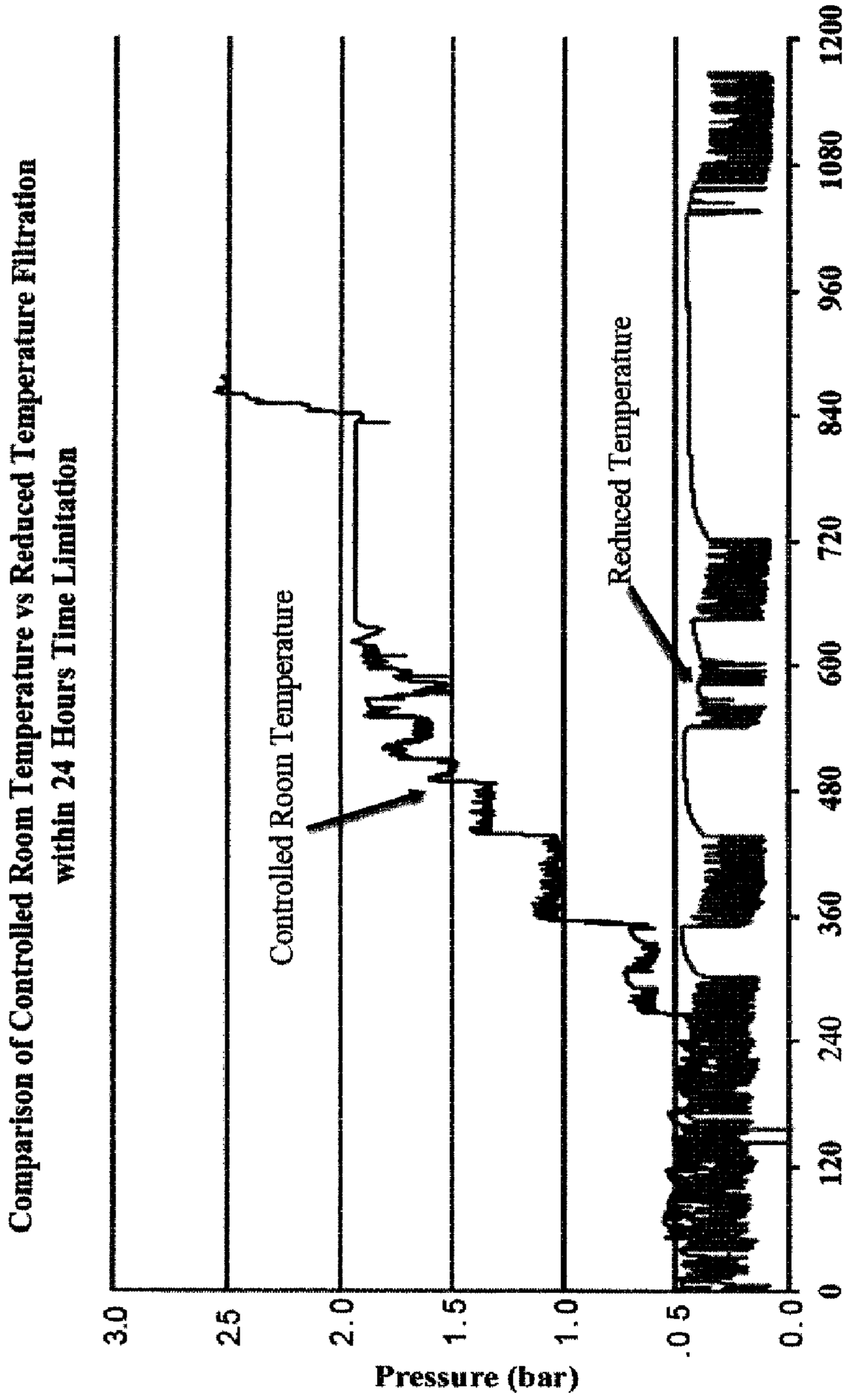
Comparison of Controlled Room Temperature vs Reduced Temperature Filtration
within 24 Hours Time Limitation
Controlled Room Temperature
Reduced Temperature
Pressure (bar)
3.0
2.5
2.0
1.5
1.0
.0.5
0.0
Time (min)
0
120
240
360
480
600
720
840
960
1080
1200

Figure 5

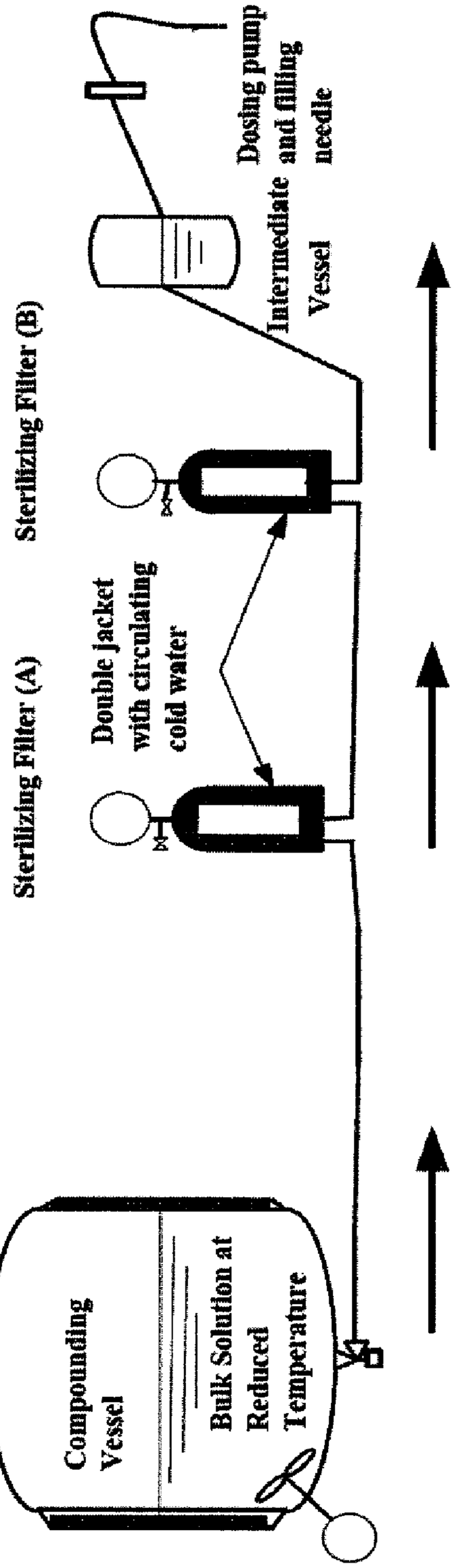
Dosing pump and filling needle
Intermediate Vessel
Sterilizing Filter (B)
Sterilizing Filter (A)
Double jacket with circulating cold water
Compounding Vessel
Bulk Solution at Reduced Temperature

Figure 9

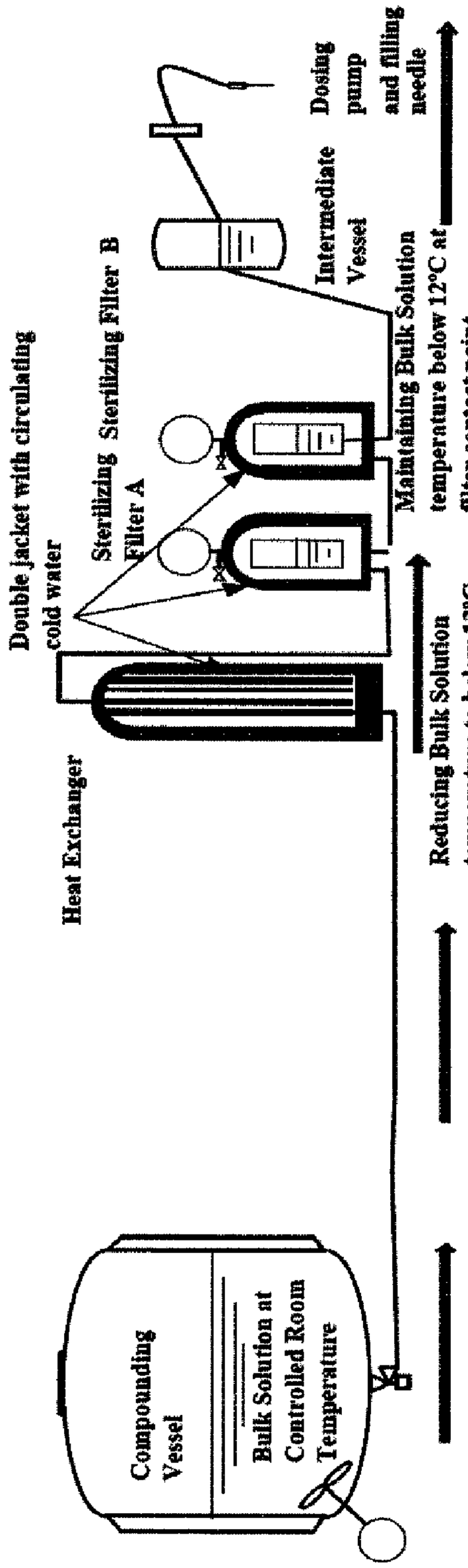
Compounding Vessel
Bulk Solution at Controlled Room Temperature
Heat Exchanger
Double jacket with circulating cold water
Sterilizing Filter A
Sterilizing Filter B
Intermediate Vessel
Dosing pump
Reducing Bulk Solution temperature to below 12°C
Maintaining Bulk Solution temperature below 12°C at filter contact point
and filling needle

Figure 7

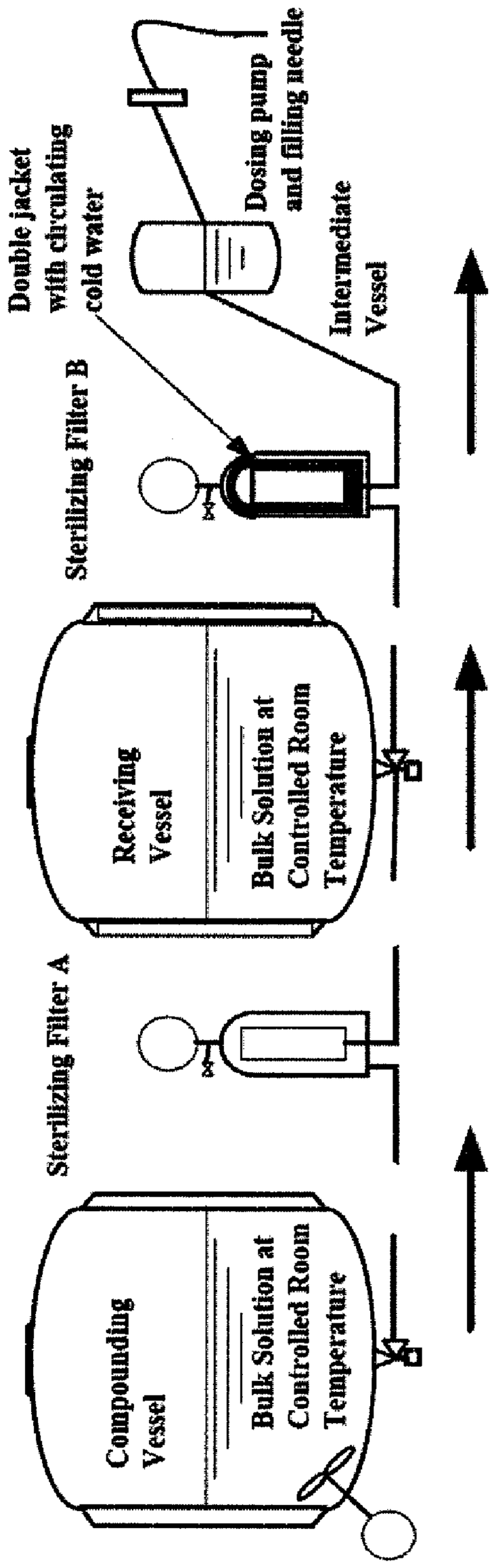
Compounding Vessel
Bulk Solution at Controlled Room Temperature
Sterilizing Filter A
Receiving Vessel
Bulk Solution at Controlled Room Temperature
Sterilizing Filter B
Double jacket with circulating cold water
Dosing pump and filling needle
Intermediate Vessel

Figure 8

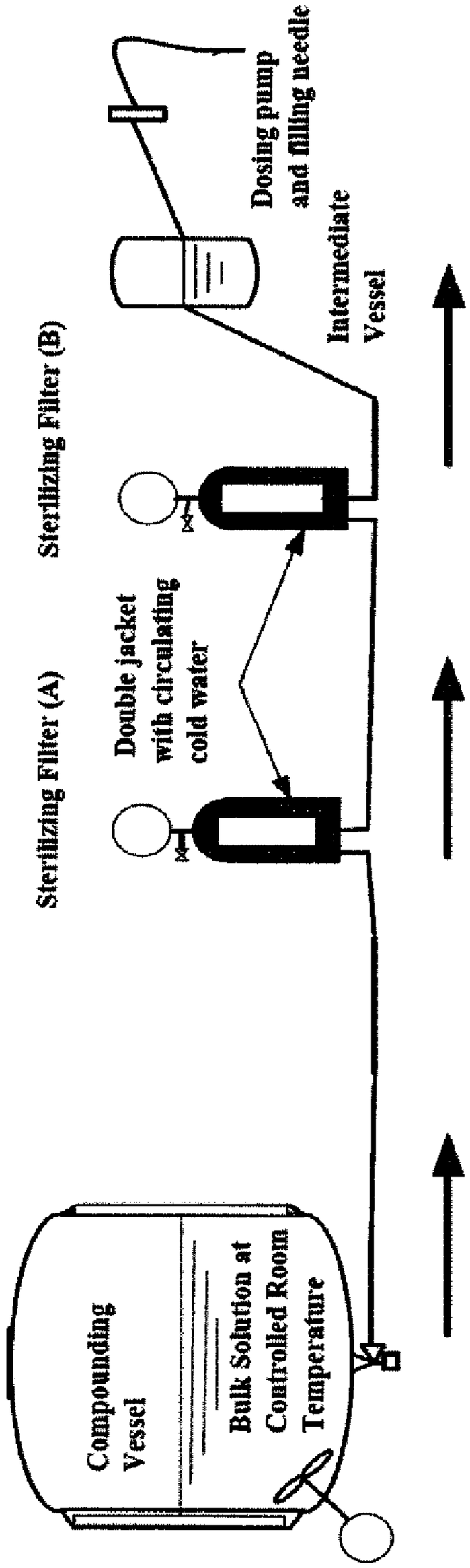
Compounding Vessel
Bulk Solution at Controlled Room Temperature
Sterilizing Filter (A)
Double jacket with circulating cold water
Sterilizing Filter (B)
Intermediate Vessel
Dosing pump and filling needle

Figure 6

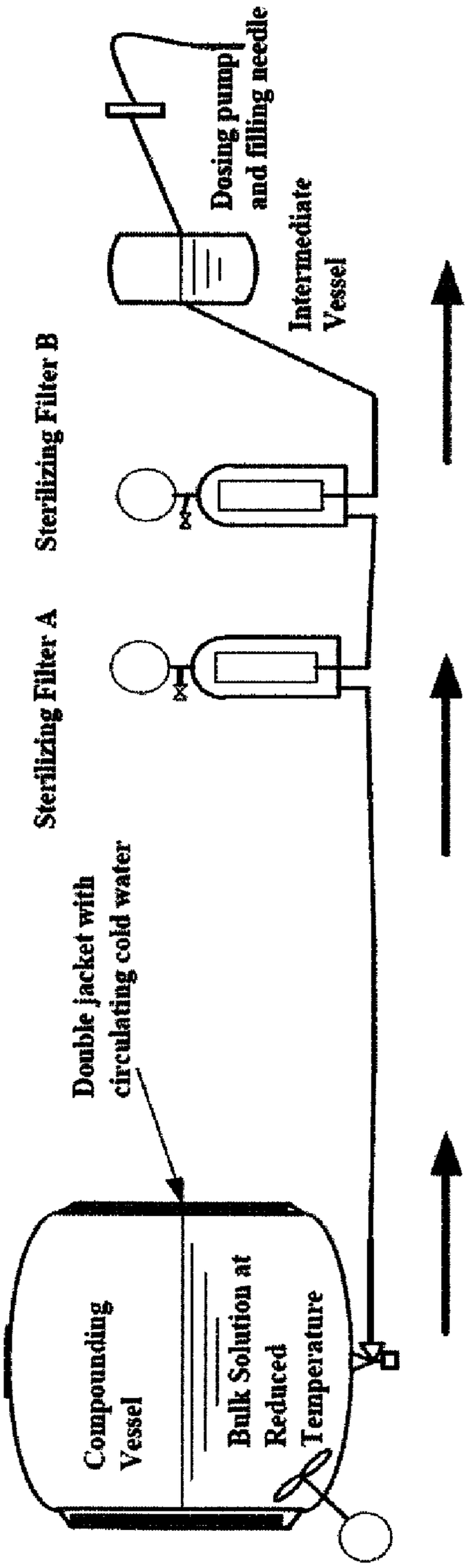
Dosing pump and filling needle
Intermediate Vessel
Sterilizing Filter B
Sterilizing Filter A
Double jacket with circulating cold water
Compounding Vessel
Bulk Solution at Reduced Temperature

Figure 10

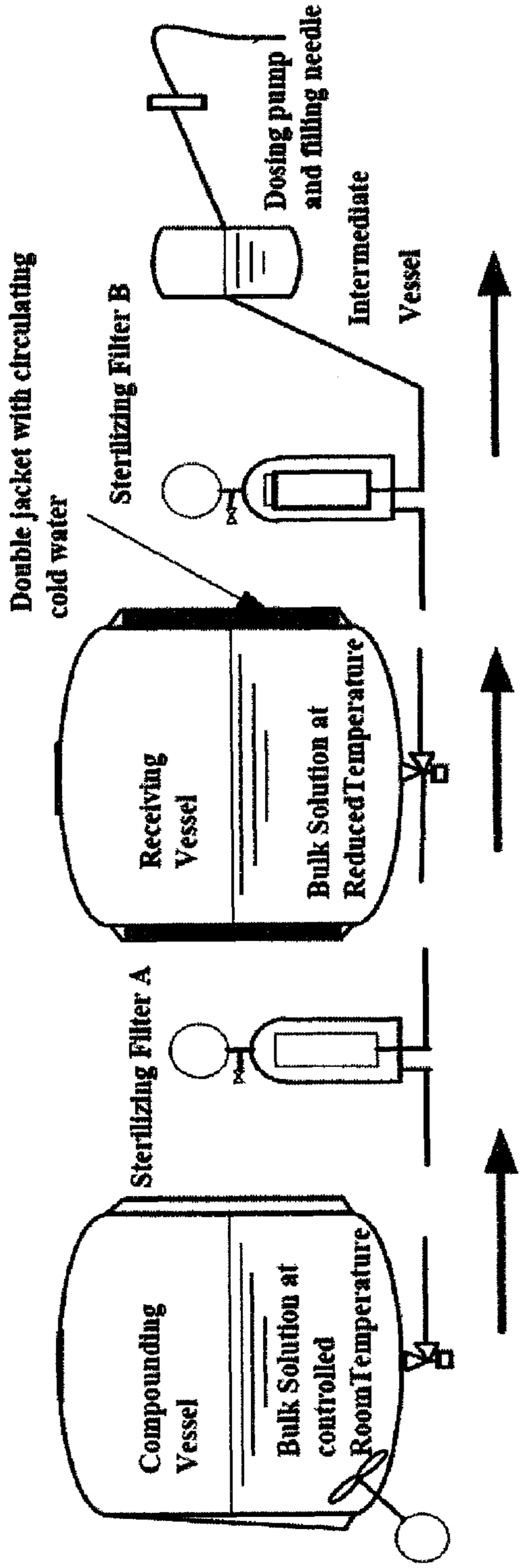
Compounding Vessel
Bulk Solution at controlled Room Temperature
Sterilizing Filter A
Receiving Vessel
Bulk Solution at ReducedTemperature
Double jacket with circulating cold water
Sterilizing Filter B
Intermediate Vessel
Dosing pump and filling needle

Figure 11

PROCESS FOR MANUFACTURING GLATIRAMER ACETATE PRODUCT

RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 14/608,126, filed Jan. 28, 2015, now allowed, the contents of which are hereby incorporated by reference in their entirety into this application.

The disclosures of various publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

Glatiramer acetate (GA), the active ingredient of Copaxone®, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The peak average molecular weight of glatiramer acetate is between 5,000 and 9,000 daltons. Glatiramer acetate is identified by specific antibodies (Copaxone, Food and Drug Administration Approved Labeling (Reference ID: 3443331) [online], TEVA Pharmaceutical Industries Ltd., 2014 [retrieved on Dec. 24, 2014], Retrieved from the Internet: <URL: www.accessdata.fda.gov/drugsatfda_docs/label/2014/020622s0891bl.pdf>).

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

(Glu,Ala,Lys,Tyr)x.X CH3COOH

$(C_5H_9NO_4.C_3H_7NO_2.C_6H_{14}N_2O_2.C_9H_{11}NO_3).xC_2H_4O_2$

CAS-147245-92-9

Copaxone® is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of Copaxone® solution contains 20 mg or 40 mg of GA, the active ingredient, and 40 mg of mannitol. The pH of the solutions is approximately 5.5 to 7.0. Copaxone® 20 mg/mL in a prefilled syringe (PFS) is an approved product, the safety and efficacy of which are supported by over two decades of clinical research and over a decade of post-marketing experience. Copaxone® 40 mg/mL in a PFS was developed as a new formulation of the active ingredient GA. Copaxone® 40 mg/mL is a prescription medicine used for the treatment of people with relapsing forms of multiple sclerosis (Copaxone, Food and Drug Administration Approved Labeling (Reference ID: 3443331) (online), TEVA Pharmaceutical Industries Ltd., 2014 [retrieved on Dec. 24, 2014], Retrieved from the Internet: <URL: www.accessdata.fda.gov/drugsatfda_docs/label/2014/020622s0891bl.pdf>).

It is an object of the present invention to provide an improved process for manufacturing GA drug products.

SUMMARY OF THE INVENTION

The patent provides a process of preparing a pharmaceutical preparation of glatiramer acetate and mannitol in a suitable container comprising the steps of:

(i) obtaining an aqueous pharmaceutical solution of glatiramer acetate and mannitol;

(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

This patent also provides a prefilled syringe containing 40 mg of glatiramer acetate and 40 mg mannitol, which syringe is prepared by a process of the invention.

This patent further provides an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol, wherein the aqueous pharmaceutical solution

a) has a viscosity in the range of 2.0-3.5 cPa; or

b) has an osmolality in the range of 275-325 mosmol/Kg.

This patent also provides a prefilled syringe containing 1 ml of an aqueous pharmaceutical solution prepared by a process of the invention.

This patent also provides an automated injector comprising the prefilled syringe prepared by a process of the invention.

Aspects of the present invention relate to a method of treatment of a human patient suffering from a relapsing form of multiple sclerosis comprising administration to the human patient of three subcutaneous injections of a 40 mg/ml dose of glatiramer acetate per week using the prefilled syringe of this invention, using the aqueous pharmaceutical solution of this invention, or using the automated injector of this invention so as to treat the human patient.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Schematic description of filtration process by cooled receiving vessel and filter housing.

FIG. **2**. Schematic description of filtration process by heat exchanger and cooled filter housing.

FIG. **3**. Pressure record for Experiment No. 1. * Filtration of GA solution at controlled room temperature was stopped and the remaining solution was transferred to the cooled receiving vessels.

FIG. **4**. Pressure record for Experiment No. 2. * Pauses of 3 hours and 5 hours for GA solutions filtered at controlled room temperature and at reduced temperature, respectively. ** Pause of 10 hours for both GA solutions. *** Filtration of GA solution at controlled room temperature was stopped. Remaining GA solution was filtered at reduced temperature.

FIG. **5**. Pressure record for Experiment No. 3.

FIG. **6**. Schematic description of filtration process by cooled compounding vessel and cooled filter housings on both Filter A and Filter B.

FIG. **7**. Schematic description of filtration process by heat exchanger and cooled filter housings on both Filter A and Filter B.

FIG. **8**. Schematic description of filtration process by cooled filter housing on only Filter B.

FIG. **9**. Schematic description of filtration process by cooled filter housings on both Filter A and Filter B.

FIG. **10**. Schematic description of filtration process by cooled compounding vessel.

FIG. **11**. Schematic description of filtration process by cooled receiving vessel.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a process of preparing a pharmaceutical preparation of glatiramer acetate and mannitol in a suitable container comprising the steps of:

(i) obtaining an aqueous pharmaceutical solution of glatiramer acetate and mannitol;

(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

In some embodiments the filtering step (ii) comprises filtering the aqueous pharmaceutical solution through a first filter, or a first filter and a second filter.

In some embodiments the process further comprises the step of reducing the temperature of the second filter to a temperature from above 0° C. up to 17.5° C.

In some embodiments the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. before passing through the second filter.

In some embodiments the filtering step (ii) further comprises the step of receiving the aqueous pharmaceutical solution filtered through the first filter in a receiving vessel.

In same embodiments the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. after leaving the receiving vessel and before entering into the second filter.

In some embodiments the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. while in the receiving vessel.

In some embodiments the process further comprises the step of reducing the temperature of the first filter to a temperature from above 0° C. up to 17.5° C.

In some embodiments the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. before passing through the first filter.

In some embodiments the obtaining step (i) comprises compounding the aqueous pharmaceutical solution in a compounding vessel.

In some embodiments the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. after leaving the compounding vessel and before entering into the first filter.

In some embodiments the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. while in the compounding vessel.

In some embodiments the aqueous pharmaceutical solution is passed through the second filter at a rate of 3-25 liters/hour.

In some embodiments the aqueous pharmaceutical solution is passed through the second filter preferably at a rate of 3-22 liters/hour.

In some embodiments the aqueous pharmaceutical solution is passed through the second filter more preferably at a rate of 3-15 liters/hour.

In some embodiments the aqueous pharmaceutical solution is passed through the second filter at a rate more preferably at a rate of 3-10 liters/hour.

In some embodiments the pressure during the filtering step (ii) and the pressure during the filling step (iii) is maintained below 5.0 bar.

In some embodiments the pressure during the filtering step (ii) and the pressure during the filling step (iii) is maintained preferably below 3.0 bar.

In some embodiments the pressure during the filtering step (ii) and the pressure during the filling step (iii) is maintained below 2.0 bar.

In some embodiments the temperature of the aqueous pharmaceutical solution is between 0° C. and 14° C., or the temperature of the aqueous pharmaceutical solution is reduced to a temperature between 0° C. and 14° C.

In some embodiments the temperature of the aqueous pharmaceutical solution is between 0° C. and 12° C., or the temperature of the aqueous pharmaceutical solution is reduced to a temperature between 0° C. and 12° C.

In some embodiments the temperature of the aqueous pharmaceutical solution is 2° C.-12° C., or the temperature of the aqueous pharmaceutical solution is reduced to 2° C.-12° C.

In some embodiments the temperature of the aqueous pharmaceutical solution is 4° C.-12° C., or the temperature of the aqueous pharmaceutical solution is reduced to 4° C.-12° C.

In some embodiments the filtering is performed using a sterilizing filter having a pore size of 0.2 μm or less, wherein the first, the second or both filters are a sterilizing filter having a pore size of 0.2 μm or less.

In some embodiments the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 20 mg/ml glatiramer acetate and 40 mg/ml mannitol.

In some embodiments the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

In some embodiments the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution having a pH in the range of 5.5-7.0.

In some embodiments the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution which is a sterilized aqueous solution which has been sterilized by filtration and without subjecting the aqueous pharmaceutical solution to heat, chemicals, or radiation exposure.

In some embodiments the pharmaceutical preparation is a lyophilized powder of glatiramer acetate and mannitol.

In some embodiments the process further comprises a step of lyophilizing the filtrate after it has been filled into the suitable container so as to form a lyophilized powder of glatiramer acetate and mannitol in the suitable container.

In some embodiments the suitable container is a syringe, vial, ampoule, cartridge or infusion.

In some embodiments the suitable container is a syringe.

In some embodiments the syringe contains 1 ml of an aqueous pharmaceutical solution.

This invention provides a prefilled syringe containing 40 mg of glatiramer acetate and 40 mg mannitol, which syringe is prepared by a process of the invention.

According to any embodiment of the prefilled syringe disclosed herein, the prefilled syringe contains 1 ml of an aqueous pharmaceutical solution of 40 mg/ml of glatiramer acetate and 40 mg/ml mannitol.

According to any embodiment of the prefilled syringe disclosed herein, the aqueous pharmaceutical solution

a) has a viscosity in the range of 2.0-3.5 cPa; or

b) has an osmolality in the range of 270-330 mosmol/Kg.

According to any embodiment of the prefilled syringe disclosed herein, the aqueous pharmaceutical solution

a) has a viscosity in the range of 2.2-3.0 cPa; or

b) has an osmolality in the range of 275-325 mosmol/Kg.

This invention provides an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol, wherein the aqueous pharmaceutical solution

a) has a viscosity in the range of 2.0-3.5 cPa; or

b) has an osmolality in the range of 275-325 mosmol/Kg.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution has a viscosity in the range of 2.0-3.5 cPa.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution has a viscosity in the range of 2.61-2.92 cPa.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution has an osmolality in the range of 275-325 mosmol/Kg.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution has an osmolality in the range of 300-303 mosmol/Kg.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution comprises glatiramer acetate having a viscosity in the range of 2.3-3.2 cPa.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution comprises glatiramer acetate having a viscosity in the range of 2.6-3.0 cPa.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution comprises glatiramer acetate having an osmolality in the range of 290-310 mosmol/Kg.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution comprises glatiramer acetate having an osmolality in the range of 295-305 mosmol/Kg.

According to some embodiments of the aqueous pharmaceutical solution, the aqueous pharmaceutical solution has a pH in the range of 5.5-7.0.

This invention provides a prefilled syringe containing 1 ml of an aqueous pharmaceutical solution prepared by the invention.

This invention provides an automated injector comprising the prefilled syringe prepared by the invention.

This invention provides a method of treatment of a human patient suffering from a relapsing form of multiple sclerosis comprising administration to the human patient of three subcutaneous injections of a 40 mg/ml dose of glatiramer acetate per week using the prefilled syringe of this invention, using the aqueous pharmaceutical solution of this invention, or using the automated injector of this invention so as to treat the human patient.

In some embodiments, the human patient is suffering from relapsing-remitting multiple sclerosis.

In some embodiments, the human patient has experienced a first clinical episode and has MRI features consistent with multiple sclerosis.

This invention provides a process of preparing a pharmaceutical preparation of glatiramer acetate and mannitol in a suitable container comprising the steps of:

(i) obtaining an aqueous pharmaceutical solution of glatiramer acetate and mannitol;

(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

In an embodiment, the filtering step (ii) comprises filtering the aqueous pharmaceutical solution through a first filter, and a second filter.

In an embodiment, the obtaining step (i) comprises compounding the aqueous pharmaceutical solution in a compounding vessel.

In an embodiment, the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. while in the compounding vessel.

In an embodiment, the process further comprises the step of reducing the temperature of the first filter to a temperature from above 0° C. up to 17.5° C.

In an embodiment, the process further comprises the step of reducing the temperature of the second filter to a temperature from above 0° C. up to 17.5° C.

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(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

In an embodiment, the filtering step (ii) comprises filtering the aqueous pharmaceutical solution through a first filter, and a second filter.

In an embodiment, the obtaining step (i) comprises compounding the aqueous pharmaceutical solution in a compounding vessel.

In an embodiment, the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. after leaving the compounding vessel and before entering into the first filter.

In an embodiment, the process further comprises the step of reducing the temperature of the first filter to a temperature from above 0° C. up to 17.5° C.

In an embodiment, the process further comprises the step of reducing the temperature of the second filter to a temperature from above 0° C. up to 17.5° C.

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(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

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In an embodiment, the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. after leaving the compounding vessel and before entering into the first filter.

In an embodiment, the process further comprises the step of reducing the temperature of the first filter to a temperature from above 0° C. up to 17.5° C.

In an embodiment, the process further comprises the step of reducing the temperature of the second filter to a temperature from above 0° C. up to 17.5° C.

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(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

In an embodiment, the filtering step (ii) comprises filtering the aqueous pharmaceutical solution through a first filter, and a second filter.

In an embodiment, the process further comprises the step of reducing the temperature of the first filter to a temperature from above 0° C. up to 17.5° C.

In an embodiment, the process further comprises the step of reducing the temperature of the second filter to a temperature from above 0° C. up to 17.5° C.

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(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

In an embodiment, the filtering step (ii) comprises filtering the aqueous pharmaceutical solution through a first filter, and a second filter.

In an embodiment, the obtaining step (i) comprises compounding the aqueous pharmaceutical solution in a compounding vessel.

In an embodiment, the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. while in the compounding vessel.

This invention provides a process of preparing a pharmaceutical preparation of glatiramer acetate and mannitol in a suitable container comprising the steps of:

(i) obtaining an aqueous pharmaceutical solution of glatiramer acetate and mannitol;

(ii) filtering the aqueous pharmaceutical solution at a temperature of from above 0° C. up to 17.5° C. to produce a filtrate; and

(iii) filling the suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

In an embodiment, the filtering step (ii) comprises filtering the aqueous pharmaceutical solution through a first filter, and a second filter.

In an embodiment, the filtering step (ii) further comprises the step of receiving the aqueous pharmaceutical solution filtered through the first filter in a receiving vessel.

In an embodiment, the process further comprises the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature from above 0° C. up to 17.5° C. while in the receiving vessel.

Automated Injection Device

The mechanical workings of an automated injection assisting device can be prepared according to the disclosure in European application publication No. EP0693946 and U.S. Pat. No. 7,855,176, which are incorporated herein by reference.

All combinations of the various elements described herein are within the scope of the invention.

DEFINITIONS

As used herein, "glatiramer acetate" is a complex mixture of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. The peak average molecular weight of glatiramer acetate is between 5,000 and 9,000 daltons. Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

(Glu,Ala,Lys,Tyr)*x*.X CH3COOH

(C5H9NO4.C3H7NO2.C6H14N2O2.C9H11NO3)
x.*x*C2H4O2

CAS-147245-92-9

As used herein "glatiramer acetate drug substance" is the glatiramer acetate active ingredient prior to its formulation into a glatiramer acetate drug product.

As used herein, a "glatiramer acetate drug product" is a formulation for pharmaceutical use which contains a glatiramer acetate drug substance. Copaxone® is a commercial glatiramer acetate drug product manufactured by TEVA Pharmaceutical Industries Ltd. (Israel), which is described in Copaxone, Food and Drug Administration Approved Labeling (Reference ID: 3443331) [online], TEVA Pharmaceutical Industries Ltd., 2014 [retrieved on Dec. 24, 2014], Retrieved from the Internet: <URL: www.accessdata.fda.gov/drugsatfda_docs/label/2014/020622s0891bl.pdf>, the contents of which are hereby incorporated by reference. Copaxone® is available as 20 mg/mL administered once per day, and/or 40 mg/ml administered three times per week.

As used herein, a "sterilizing filter" is a filter with a pore size of 0.2 μm or less which will effectively remove microorganisms.

By any range disclosed herein, it is meant that all hundredth, tenth and integer unit amounts within the range are specifically disclosed as part of the invention. Thus, for example, 1 mg to 50 mg means that 1.1, 1.2 . . . 1.9; and 2, 3 . . . 49 mg unit amounts are included as embodiments of this invention.

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

EXPERIMENTAL DETAILS

Methods

Glatiramer Acetate (GA) Injection 40 mg/mL in a prefilled syringe (GA injection 40 mg/mL in PFS or Copaxone® 40 mg/mL) was developed as a new formulation of the active ingredient glatiramer acetate, which is also used in the marketed product Copaxone 20 mg/mL solution for injection in a prefilled syringe. Copaxone® 40 mg/mL is to be administered three times a week by subcutaneous injection to patients with Relapsing Remitting Multiple Sclerosis. The new formulation is based on the formulation of the marketed

Copaxone® 20 mg/mL solution for injection in a prefilled syringe. Copaxone® 20 mg/mL is an approved product, the safety and efficacy of which are supported by over two decades of clinical research and over a decade of post-marketing experience. The only difference between the formulations is the double amount of the active substance used, which results in a solution with double the concentration of glatiramer acetate (40 mg/mL vs. 20 mg/mL). The amount of mannitol in both Copaxone® formulations remains unchanged (40 mg/mL).

The compositions of Copaxone® 20 mg/mL and Copaxone® 40 mg/mL are detailed in Table 1.

TABLE 1

Compositions of Copaxone ® 20 mg/mL and Copaxone ® 40 mg/mL

Components	Copaxone ® 20 mg/mL Content per mL	Copaxone ® 40 mg/mL Content per mL
Glatiramer Acetate[1]	20.0 mg	40.0 mg
Mannitol USP/Ph. Eur.	40.0 mg	40.0 mg
Water for Injection USP/Ph. Eur/JP	q.s. to 1.0 mL	q.s. to 1.0 mL

[1]Calculated on the dry basis and 100% assay

Studies were conducted in order to verify that the formulation of Copaxone® 40 mg/mL, its manufacturing process and chemical, biological and microbiological attributes are appropriate for commercialization. Studies were also conducted to confirm the suitability of the proposed container closure system for packaging Copaxone® 40 mg/mL.

Mannitol was chosen as the tonicity agent for the initially formulated Copaxone® (freeze dried product, reconstituted prior to administration) as it is also a bulking agent. When the currently marketed ready-to-use formulation of Copaxone® 20 mg/mL solution for injection prefilled syringe was developed, mannitol was used in this formulation as well, as the osmoregulator. Finally, when the new 40 mg/mL formulation was developed, based on the Copaxone® 20 mg/mL formulation, mannitol remained as the osmoregulator.

Mannitol is widely used in parenteral formulations as an osmoregulator. It is freely soluble in water and stable in aqueous solutions. Mannitol solutions may be sterilized by filtration. In solution, mannitol is not affected by atmospheric oxygen in the absence of catalysts. The concentration of mannitol in the Copaxone® 40 mg/mL is 40 mg/mL. Maintaining the mannitol concentration in Copaxone® 40 mg/mL resulted in an essentially isotonic solution.

Water for injection (WFI) is the most widely used solvent and inert vehicle in parenteral formulations. Water is chemically stable in all physical states. It is the base for many biological life forms, and its safety in pharmaceutical formulations is unquestioned.

Example 1

The manufacturing process of Copaxone® 40 mg/mL comprises:

- Compounding a bulk solution of GA and mannitol in water for injections (WFI).
- Sterilizing filtration of the bulk solution yielding the sterile GA solution in bulk.
- Aseptic filling of sterile bulk solution into syringe barrels and stoppering.
- Inspection and final assembly of the filled syringes.

Initially, filtration of bulk solution from the compounding vessel was performed through a sequential filter train consisting of two sequential sterilizing filters (filters named A_1 and A_2, respectively) to a receiving vessel. From the receiving vessel it was transferred to the intermediate vessel in the filling machine and further through dosing pumps and needles into prefilled syringes. However, due to a Health Authority request to place the sterilizing filter as close as possible to the filling point, the second sterilizing filter was moved between the receiving and intermediate vessels. In the current filtration train, the first sterilizing filter was named Filter A, and the second relocated sterilizing filter was named Filter B. See, FIG. **1**.

In line with the process for the approved Copaxone® 20 mg/mL formulation, all processing steps of the new Copaxone® 40 mg/mL formulation were originally conducted at controlled room temperature. However, filtration of the higher concentration solution resulted in a pressure build-up on the second filter, Filter B. Despite the observed pressure increase on Filter B, a high-quality drug product could be obtained by filtration of GA 40 mg/mL at controlled room temperature, as confirmed by release and stability data. Nevertheless, an improved filtration process was needed which avoided the build-up on the second filter.

Flow rate for fluids can be defined by the differential pressure, and inversely moderated by viscosity. Viscosity, in turn, is usually reciprocal in relation to temperature (Meltzer and Jornitz, *Filtration and Purification in the Biopharmaceutical Industry*, Second Edition, CRC Press, 2007, page 166). Increasing the temperature of a solution will normally decrease the viscosity, thereby enhancing the flow rate.

In an attempt to solve the pressure build-up problem on the second filter, the temperature condition of the filtration was raised above controlled room temperature. Although the viscosity decreased, the filterability decreased, resulting in a failed attempt.

The following studies were performed:

- Filter Validation Study: Determination of ranges for the manufacturing parameters related to sterilizing Filter A and sterilizing Filter B of the bulk solution, as well as confirmation of filter compatibility with the drug product.
- Filtration Process: Selection of the sterilizing filtration conditions best suitable for the manufacturing process and the quality of the drug product.

Filters Used for Copaxone® 20 mg/mL and Copaxone® 40 mg/mL Manufacturing

The manufacturing process of Copaxone® 40 mg/mL was based on the process used to produce the marketed Copaxone® 20 mg/mL solution for injection in a prefilled syringe. Therefore the same filters used for filtration of marketed product were used.

Two sterilizing filters were used, each of which having a pore size of 0.2 μm or less, to effectively remove microorganisms. Sterilization is achieved only by filtration using sterilizing filters and not by using other methods, e.g. sterilization is achieved without using heat, chemicals, or radiation exposure.

Filter Validation Study—Confirmation and Setting of Parameters Associated with Filter Compatibility and with Sterilizing Filtration

The following tests were performed in order to confirm the filter validity:

- Extractables testing—assessment of extractables released from the filter upon steam sterilization and their removal from the filter by a model solvent, thus assess-

ing the volume to be discarded after the filtration through the Filter B, prior to beginning of the aseptic filling.

Compatibility/adsorption testing—assessment of the chemical compatibility of GA 20 mg/mL and GA 40 mg/mL solution with the filter material and the extent of its adsorption to the filter, thus assessing the volume to be discarded after the filtration through Filter B, prior to beginning of the aseptic filling in order to provide assay within specifications.

Residual effect—To ensure that no significant residual GA 20 mg/mL or GA 40 mg/mL solution that might affect the post use integrity test remains on the filter after filtration.

Bacterial challenge—To ensure that the filtration process does not affect the ability of the filter to provide a sterile solution.

The above tests were conducted using maximum pressure (up to 5.0 bar). The validation study demonstrated that the selected filtration system is capable of providing a high quality Copaxone® 20 mg/mL and Copaxone® 40 mg/mL.

Given the strict and well-defined operational and equipment parameters of the GA 40 mg/mL solution filtration process, a plan to mitigate the potential increase in pressure by reducing the filtration temperature was developed.

Without much expectations, it was decided to examine the filtration process of GA 40 mg/mL sterile bulk solution through Filter B under reduced temperature conditions, using the same filters and filtration train as for the filtration at controlled room temperature.

Accordingly, experiments were performed in order to compare the filtration of GA 40 mg/mL sterile bulk solution through Filter B under reduced temperature and controlled room temperature in the production environment and to ensure that there is no difference with regard to the quality and stability profiles of the filtered solutions. In all experiments, the sterile bulk solution was prepared according to the standard compounding and filtration train (see FIG. **1**) and filtered through two filters: Filter A and Filter B.

The experiments tested two different cooling technologies (cooled receiving vessels vs heat exchanger) with cooled filter. The studies are schematically depicted in FIG. **1** and FIG. **2**. Further details about these experiments and their outcomes are provided hereafter.

Filtration Process—Experiment No. 1

The objective of Experiment No. 1 was to compare the filterability of a batch of bulk solution held and filtered through Filter B at either controlled room temperature or under reduced temperature conditions (cooling by double-jacketed receiving vessel and cooled Filter B housing).

The study is schematically depicted in FIG. **1**. The experimental design and the obtained results are summarized in Table 2 and FIG. **3**.

TABLE 2

Experimental Design and Results for Experiment No. 1.

Experiment Outline	Reduced Temperature Filtration	Controlled Room Temperature Filtration
Compounding	According to standard manufacturing procedure[1]	
Holding time in the receiving vessel	13 hours	13 hours
Temperature of solution held in the receiving vessel	6.6-10.7° C.[2]	17.8-24.6° C.
Planned regimen for filtration though Filter B[3]	Intermittent filtration: Stage I - 5 filtration steps of filtration of about 10 liters of bulk solution - followed by pauses of about 50 minutes each, followed by a pause of 5 hours. Stage II - 4 filtration steps of filtration of about 10 liters of bulk solution - followed by pauses of about 50 minutes each, followed by a pause of about 10 hours. Stage III - Filtration of remaining solution.	
Total volume of bulk solution filtered	About 125 L. Filtration was completed.	About 85 liters. Filtration was stopped due to increase in pressure on Filter B.

[1]One bulk solution was prepared and divided into two portions. Bulk solution size: 230 liters. Filtration of solution at controlled room temperature was stopped after 85 liters have been pushed through the filter due to increased pressure and the remaining solution was transferred to the cooled receiving vessels.

[2]The temperature increased (to 14.9° C.) once during the filtration following the addition of the remaining solution kept at ambient temperature.

[3]The filtrations were carried out in parallel.

Surprisingly, filtration at reduced temperature allowed filtration to be completed without the pressure increase associated with filtration at controlled room temperature.

Example 2

Filtration Process—Experiment No. 2

The first objective of Experiment No. 2 was to evaluate whether local cooling of GA 40 mg/mL solution using a Heat Exchanger (HE) could improve the filterability through cooled Filter B compared to filterability of the same bulk solution at controlled room temperature.

The second objective of Experiment No. 2 was to confirm that there is no difference in the quality of the drug product filled into syringes at controlled room temperature and drug product filled into syringes at reduced temperature.

Cooling by heat exchanger was evaluated as it seemed to be much easier to steam sterilize than using the double jacketed receiving vessels. The HE was located between the receiving vessel and Filter B. Consequently, as opposed to Experiment No. 1 (in which the solution was cooled by the double-jacketed receiving vessels following filtration through Filter A and kept cooled prior to filtration through Filter B), the solution in this experiment was held at controlled room temperature prior to filtration of the locally cooled (by HE) GA solution through Filter B.

The study is schematically depicted in FIG. **2**. The experimental design and the obtained results are summarized in Table 3. The pressure observed over the course of the filling process of Experiment No. 2 is shown in FIG. **4**.

TABLE 3

Experimental Design and Results for Experiment No. 2.

Experiment Outline	Reduced Temperature Filtration	Controlled Room Temperature Filtration
Compounding	According to standard manufacturing procedure[1]	
Filtration into a receiving vessel	Filtration of all the bulk solution through Filter A into a receiving vessel held at controlled room temperature	
Temperature of solution held in the receiving vessel	Controlled room temperature	
Holding time in the receiving vessel	19 hours	
Planned regimen for filtration through Filter B	The solution is locally cooled as it is transferred through a HE and filtered through cooled Filter B. Three consecutive filtration and filling stages. About 3 hours break between Stage I and Stage II and about 10 hours break between Stage II and Stage III.	The solution is filtered through Filter B at controlled room temperature. Three consecutive filtration and filling stages. About 5 hours break between Stage I and Stage II and about 10 hours break between Stage II and Stage III.
Temperature of solution transferred through the HE	6.4-12° C.	No use of HE
Duration of filtration through Filter B[2]	24 hours	19 hours
Temperature of solution transferred through Filter B	5.7-8.8° C.	Ambient temperature
Total volume of bulk solution filtered and filled into syringes	154 L	63 L[3]
Storage conditions during stability studies	Long term (2-8° C.) Accelerated (25° C./60% RH) - completed 6 months Stress (40° C./75% RH) - completed 3 months	
Stability data	The stability data showed that the drug product has a similar stability profile when it is filtered at controlled room temperature or under reduced temperature conditions. Both filtration processes demonstrate similar impurity profiles.	

[1]One bulk solution was prepared and divided into two portions. Bulk solution size: 230 liters.
[2]Both filtration processes (reduced and controlled room temperature) were carried out in parallel for comparison. At each stage, filtration was carried out at controlled room temperature, followed by filtration at reduced temperature.
[3]Filtration of solution at controlled room temperature was stopped due to pressure increase and the remaining solution was filtered at reduced temperature.

Example 3

Filtration Process—Experiment No. 3

One objective of Experiment No. 3 was to confirm whether cooling of GA 40 mg/mL bulk solution prior to filtration, using HE and cooled filter housing, allows filtration and filling of batches of 130 L size within various manufacturing regimens.

Another objective of Experiment No. 3 was to evaluate the influence of holding time at various stages of the manufacturing process on filterability of GA 40 mg/mL.

Another objective of Experiment 3 was to demonstrate with a high degree of assurance that locally cooled GA 40 mg/mL solution filtered through Filter B is not different in its quality and stability profile from GA 40 mg/mL solution filtered through Filter B at controlled room temperature conditions with regard to pre-determined parameters and limits.

A series of three batches of bulk solution, manufactured at various regimens, were prepared. Each bulk solution was prepared from an identical combination of the same three drug substance batches.

The experimental design and results are summarized in Table 4.

TABLE 4

Experimental Design and Results for Experiment No. 3

Experiment Outline	Reduced Temperature Filtration	Controlled Room Temperature Filtration	Reduced Temperature Filtration	Controlled Room Temperature Filtration
Batch No.	A	A-2[1]	B	C
Compounding	Standard compounding	Standard compounding	Standard compounding	Standard compounding
Batch size	First 130 L from bulk solution A	Remaining 50 L from bulk solution A	180 L	180 L
Holding time in the compounding vessel[2]	4 hours	4 hours (same bulk solution as A)	8 hours	3.5 hours
Holding time in the receiving vessel[3]	1.5 hours	10.5 hours[4]	16 hours	13 hours
Duration of filtration through Filter B	7 hours	3 hours	19.5 hours	13 hours
Total duration of entire process (total holding time)	12.5 hours	17.5 hours	43.5 hours	29.5 hours

TABLE 4-continued

Experimental Design and Results for Experiment No. 3

Experiment Outline	Reduced Temperature Filtration	Controlled Room Temperature Filtration	Reduced Temperature Filtration	Controlled Room Temperature Filtration
Temperature range before Filter B	10.4-12.2° C.	Controlled room temperature	10.2-11.7° C.	Controlled room temperature
Temperature range after Filter B	9.3-11.0° C.	Controlled room temperature	9.0-10.2° C.	Controlled room temperature
Maximum pressure before Filter B	0.6 bar	0.3 bar	0.6 bar	2.5 bar[5]
Total volume filled into syringes	130 L	50 L	180 L	134 L
Storage conditions during stability studies	Long term (2-8° C.)	Stress (40° C./60% RH)	Long term (2-8° C.)	Long term (2-8° C.)
	Accelerated (25° C./60% RH)		Accelerated (25° C./60% RH)	Accelerated (25° C./60% RH)
	Stress (40° C./60% RH)		Stress (40° C./60% RH)	Stress (40° C./60% RH)
Stability data and conclusions	Stability data showed that the drug product has a similar stability profile at all three storage conditions, regardless of whether it is filtered at controlled room temperature or under reduced temperature conditions. Both filtration processes result in product having substantially the same degradation and impurity profile at stress conditions.			

[1]Batches A and A-2 are from the same bulk solution. Filter B was replaced with a new filter prior to filtration of A-2.

[2]Compounding and subsequent holding time in the compounding vessel (incl. filtration through filter A).

[3]Time from end of filtration through Filter A to beginning of filtration through Filter B and filling.

[4]Since A-2 was filtered and filled into syringes subsequent to the filtration and filling of A, the stated holding time represents the sum of the holding time of A in addition to the time A-2 was held until the filtration at controlled room temperature was initiated.

[5]Throughout the filling, gradual increase of filtration pressure was required in order to maintain flow rate that would correspond to the rate required for continuous filling.

Based on the results of Experiment No. 3, it was confirmed that local cooling by heat exchanger is sufficient in order to enable filtration of a 130 L batch. In addition, the quality and stability profile of GA 40 mg/mL solutions filtered at controlled room temperature and reduced temperature were found to be substantially identical.

Example 4

Cooling of GA 40 mg/mL bulk solution below 17.5° C. in the compounding vessel before passing through cooled Filter A and cooled Filter B in sequence (see FIG. **6**) results in lower pressure during the filtration step of both Filter A and Filter B as compared to the holding the same bulk solution in the compounding vessel and passing it through Filter A and Filter B at controlled room temperature (Cooling of the bulk solution by using double jacketed compounding vessel and cooling the filters by using double jacketed filter housings).

Reducing the temperature of the GA 40 mg/mL bulk solution in the compounding vessel and passing it through cooled Filter A and Filter B in sequence (see FIG. **6**) significantly reduces impairment of filterability caused by the total duration of the process (holding time) as well as by filtering larger volume, compared to the same bulk solution held and filtered under controlled room temperature.

Example 5

Local cooling of GA 40 mg/mL bulk solution by a heat exchanger and passing the solution through cooled Filter A and cooled Filter B in sequence (see FIG. **7**) results in lower pressure during the filtration step of both Filter A and Filter B as compared to passing the same bulk solution held and filtered under controlled room temperature.

Reducing the temperature of the GA 40 mg/mL bulk solution using a heat exchanger and passing it through cooled Filter A and cooled Filter B in sequence (see FIG. **7**) significantly reduces impairment of filterability caused by the total duration of the process (holding time) as well as by filtering larger volume, compared to the same bulk solution held and filtered under controlled room temperature.

Example 6

Passing the sterilized GA 40 mg/mL bulk solution from the receiving vessel through cooled Filter B (see FIG. **8**) significantly results in lower pressure during the filtration step compared to passing the same bulk solution filtered through Filter B under controlled room temperature.

Passing the sterilized GA 40 mg/mL bulk solution from the receiving vessel through cooled Filter B (see FIG. **8**) significantly reduces impairment of filterability caused by the total duration of the process (holding time) as well as by filtering larger volume, compared to the same bulk solution held and filtered under controlled room temperature.

Example 7

Passing GA 40 mg/mL bulk solution from the compounding vessel through cooled Filter A and cooled Filter B in sequence (see FIG. **9**) results in lower pressure during the filtration step of both Filter A and Filter B as compared to passing the same bulk solution filtered under controlled room temperature.

Passing GA 40 mg/mL bulk solution from the receiving vessel through cooled Filter A and Filter B in sequence (see FIG. **9**) significantly reduces impairment of filterability caused by the total duration of the process (holding time) as well as by filtering larger volume, compared to the same bulk solution filtered under controlled room temperature.

Example 8

Cooling of GA 40 mg/mL bulk solution below 17.5° C. in the compounding vessel before passing through Filter A and Filter B in sequence (see FIG. **10**) results in lower pressure during the filtration step of both Filter A and Filter B as compared to the holding the same bulk solution in the compounding vessel and passing it through Filter A and Filter B at controlled room temperature (Cooling of the bulk solution by using double jacketed compounding vessel).

Reducing the temperature of the GA 40 mg/mL bulk solution in the compounding vessel and passing it through Filter A and Filter B in series (see FIG. **10**) significantly reduces impairment of filterability caused by the total duration of the process (holding time) as well as by filtering larger volume, compared to the same bulk solution held and under controlled room temperature.

Example 9

Cooling of GA 40 mg/mL bulk solution below 17.5° C. in the receiving vessel before passing through Filter B (see FIG. **11**) results in lower pressure during the filtration step of Filter B as compared to the holding the same bulk solution in the compounding vessel at controlled room temperature (Cooling of the bulk solution by using double jacketed compounding vessel).

Reducing the temperature of the GA 40 mg/mL bulk solution in the receiving vessel (see FIG. **10**) significantly reduces impairment of filterability caused by the total duration of the process (holding time) as well as by filtering larger volume, compared to the same bulk solution held under controlled room temperature.

Discussion of Examples 1-9

Reducing the temperature of GA 40 mg/mL sterile bulk solution significantly improved its filterability, as demonstrated by the much lower increase in pressure on Filter B during filtration and filling and by the larger volume that can be filtered at reduced temperature. Pressure increases were observed when the sterile bulk solution was held and filtered at controlled room temperature, while there was no significant increase in the pressure when the solution was filtered under reduced temperature conditions.

The holding time of the bulk solution during filtration through Filter B negatively affects the filterability of the solution. However, the total duration of the process (holding time) impaired the filterability significantly less when filtration was performed under reduced temperature conditions. Consequently, longer holding time can be used with reduced temperature filtration.

Both cooling of the solution by passing it through a heat exchanger (local cooling) and/or cooling of the whole bulk (e.g. by double-jacketed receiving vessel) before filtration through cooled Filters A or B or A and B were found to be suitable solutions for reduced temperature filtration.

Accumulated stability data indicate that there is no substantial difference with regard to quality and stability profile between the solution filtered under reduced temperature conditions and the solution filtered at controlled room temperature.

In sum, the performed experiments show that reduced temperature filtration through Filter B significantly improved the filterability of GA 40 mg/mL solution compared to the filterability of the solution when filtered at controlled room temperature. Moreover, reducing the temperature of the bulk solution during the compounding stage or before passing through Filter A, or reducing the temperature of Filter A also improves the filterability of GA 40 mg/mL solution compared to the filterability of the solution at controlled room temperature.

Consequently, the proposed manufacturing process for commercial batches of GA 20 mg/mL and GA 40 mg/mL includes cooling of the solution prior to filtration of the bulk solution through Filter B.

Example 10

Container Closure System

The container closure systems selected for the Copaxone® 40 mg/mL are the same as those used for the marketed product Copaxone® 20 mg/mL PFS. The container closure system consists of a colorless glass barrel, a plastic plunger rod and a grey rubber stopper.

Long Term and Accelerated Stability Studies

Satisfactory stability data after up to 36 months storage under long-term storage conditions (5° C.±3° C.) and after 6 months storage under accelerated conditions (25°±2° C./60±5% RH) are available. The data demonstrate that the proposed container closure systems are suitable for protection and maintenance of the drug product quality throughout its proposed shelf-life.

Protection from Light

Marketed Copaxone® should be stored protected from light. Based on this recommendation, it is proposed that Copaxone® 40 mg/mL be similarly packed in PVC transparent blisters inside a carton box, which provides light protection. The light protection of the proposed packaging when used for the Copaxone® 40 mg/mL is recommended in accordance with the results obtained from a photostability study comparing the following packaging configurations:

1. Glass barrel syringe and plunger rod (Primary package);

Glass barrel syringe and plunger rod in a transparent blister (partial secondary package);

Glass barrel syringe and plunger rod in a transparent blister inside carton box (complete intended packaging configuration).

As a reference, the following configurations were added:

2. Glass barrel syringe and plunger rod wrapped in aluminum foil;

Glass barrel and plunger rod in a transparent blister wrapped in aluminum foil.

All packages were simultaneously exposed to standardized sunlight (5 KLUX) for 10 days and to near UV light for additional 5 days.

All the obtained results from the photostability study are within the specifications. However, the impurity peak detected is lower when the drug product is packed in its complete packaging configuration. The carton box was shown to improve the photostability and gives light protection as good as that of aluminum foil, which is regarded as a complete light protector. The intended packaging configuration is therefore considered suitable for its use.

A storage statement to protect the product from light exposure should be added to the product label.

Microbiological Attributes

The medicinal product is a sterile, single dose, parenteral dosage form. Sterilization is achieved by sterile filtration.

A microbial limits test is performed for the drug substance. The sterility and bacterial endotoxins are monitored upon release and throughout stability studies of the drug product, using pharmacopoeia methods. The limits applied are identical to those applied for the marketed Copaxone®.

The same container closure systems are used for the Copaxone® 20 mg/mL and Copaxone® 40 mg/mL. The integrity testing studies performed to demonstrate the efficacy of the container closure systems on use for the marketed product are also considered relevant for Copaxone® 40 mg/mL.

Example 11

Viscosity

The average viscosity of batches of Copaxone® 20 mg/mL filtered under controlled room temperature and the average viscosity of batches of Copaxone® 40 mg/mL filtered under reduced temperature were obtained and compared. The average viscosity of different batches of Copaxone® 20 mg/mL filtered under controlled room temperature are reported in Table 5. The average viscosity of different batches of Copaxone® 40 mg/mL filtered under reduced temperature are reported in Table 6.

TABLE 5

Viscosity of Batches of Copaxone ® 20 mg/mL Filtered Under Controlled Room Temperature

Batch No.	Average Viscosity [cPa]	Standard Deviation
1	1.92[1]	0.03
2	1.58[1]	0.00
3	1.58[1]	0.00
4	1.57[2]	0.00
5	1.67[2]	0.01
Water for Injection	0.93[2]	0.00
Average	1.664	

[1]Each value is an average of 3 individual results. Values obtained using Rheocalc V2.5 Model LV, Spindle CP40, speed 80 rpm, Shear Rate 600 1/sec, Temperature 25° C. ± 0.1
[2]Each value is an average of 6 individual results. Values obtained using Rheocalc V2.5 Model LV, Spindle CP40, speed 80 rpm, Shear Rate 600 1/sec, Temperature 25° C. ± 0.1

TABLE 6

Viscosity of Batches of Copaxone ® 40 mg/mL Filtered Under Reduced Temperature

Batch No.	Average Viscosity [cPa][1]	Standard Deviation
1	2.82	0.000
2	2.92	0.008
3	2.91	0.010
4	2.61	0.012
5	2.61	0.004
6	2.73	0.021
7	2.61	0.016
Average	2.743	0.007

[1]Each value is an average of 6 individual results. Values obtained using Rheocalc V2.5 Model LV, Spindle CP40, speed 80 rpm, Shear Rate 600 1/sec, Temperature 25° C. ± 0.1

The osmolality of batches of Copaxone® 20 mg/mL filtered under controlled room temperature and the osmolality of batches of Copaxone® 40 mg/mL filtered under reduced temperature were measured.

Samples from each batch were tested in triplicates. The results are reported in Table 7.

TABLE 7

Osmolality of Batches of Copaxone ® 20 mg/mL Filtered Under Controlled Room Temperature and Batches of Copaxone ® 40 mg/mL Filtered Under Reduced Temperature

Batch No.	GA Dose	Mannitol Dose	Average Osmolality	Relative Standard Deviation (RSD)
Copaxone ® 40 mg/mL No. 1	40 mg/ml	40 mg/ml	303 mosmol/Kg	1.2
Copaxone ® 40 mg/mL No. 2	40 mg/ml	40 mg/ml	300[1] mosmol/Kg	1.7
Copaxone ® 40 mg/mL No. 3	40 mg/ml	40 mg/ml	302 mosmol/Kg	2.1
Copaxone ® 20 mg/mL No. 1	20 mg/ml	40 mg/ml	268 mosmol/Kg	2.6
Copaxone ® 20 mg/mL No. 2	20 mg/ml	40 mg/ml	264 mosmol/Kg	1.2
Placebo	0 mg/ml	40 mg/ml	227 mosmol/Kg	0

[1]Calculated from 4 measurements.

The results show that the osmolality of batches of Copaxone® 40 mg/mL were well within the ranges of an isotonic solution. The results also show that the batches of Copaxone® 40 mg/mL conformed to the general parenteral drug product osmolality limits of 300±30 mosmol/Kg. Further, the results indicate that batches of Copaxone® 20 mg/mL were slightly hypotonic.

What is claimed:

1. A process of preparing a pharmaceutical preparation of glatiramer acetate and mannitol in a suitable container comprising the steps of:

(i) obtaining an aqueous pharmaceutical solution of glatiramer acetate and mannitol;

(ii) filtering the aqueous pharmaceutical solution through a first filter to produce a first filtrate;

(iii) filtering the first filtrate at a temperature of above 0° C. to 17.5° C. through a second filter to produce a second filtrate; and

(iv) filling the suitable container with the second filtrate obtained after performing step (iii), so as to thereby prepare the pharmaceutical preparation of glatiramer acetate and mannitol in the suitable container.

2. The process of claim **1** further comprising the step of reducing the temperature of the second filter to a temperature of above 0° C. to 17.5° C.

3. The process of claim **1** further comprising the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature of above 0° C. to 17.5° C. before passing through the second filter.

4. The process of claim **1** further comprising the step of receiving the first filtrate in a receiving vessel and reducing the temperature of the first filtrate to a temperature of above 0° C. to 17.5° C. after leaving the receiving vessel and before entering into the second filter.

5. The process of claim **1** further comprising the step of receiving the first filtrate in a receiving vessel and reducing the temperature of the first filtrate to a temperature of above 0° C. to 17.5° C. while in the receiving vessel.

6. The process of claim **1** further comprising the step of reducing the temperature of the first filter to a temperature of above 0° C. to 17.5° C.

7. The process of claim 1 further comprising the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature of above 0° C. to 17.5° C. before passing through the first filter.

8. The process of claim 1, wherein the obtaining step (i) comprises compounding the aqueous pharmaceutical solution in a compounding vessel.

9. The process of claim 8 further comprising the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature of above 0° C. to 17.5° C. after leaving the compounding vessel and before entering into the first filter.

10. The process of claim 8 further comprising the step of reducing the temperature of the aqueous pharmaceutical solution to a temperature of above 0° C. to 17.5° C. while in the compounding vessel.

11. The process of claim 1, wherein the first filtrate is passed through the second filter at a rate of 3-25 liters/hour; at a rate of 3-22 liters/hour; at a rate of 3-15 liters/hour; or at a rate of 3-10 liters/hour.

12. The process of claim 1, wherein the pressure during the filtering of step (iii) and the pressure during the filling of step (iv) is maintained below 2.0 bar.

13. The process of claim 1, wherein the temperature of the first filtrate in step (iii) is between 0° C. and 14° C., or the temperature of the first filtrate in step (iii) is reduced to a temperature between 0° C. and 14° C.

14. The process of claim 1, wherein the temperature of the first filtrate in step (iii) is between 0° C. and 12° C., or the temperature of the first filtrate in step (iii) is reduced to a temperature between 0° C. and 12° C.

15. The process of claim 1, wherein the temperature of the first filtrate in step (iii) is between 2° C. and 12° C., or the temperature of the first filtrate in step (iii) is reduced to a temperature between 2° C. and 12° C.

16. The process of claim 1, wherein the temperature of the first filtrate in step (iii) is between 4° C. and 12° C., or the temperature of the first filtrate in step (iii) is reduced to a temperature between 4° C. and 12° C.

17. The process of claim 1, wherein the filtering in step (ii), in step (iii) or both are performed using a sterilizing filter having a pore size of 0.2 μm or less.

18. The process of claim 1, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

19. A process of preparing a pharmaceutical product comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol which comprises the steps of:

(i) obtaining an aqueous pharmaceutical solution of glatiramer acetate and mannitol;

(ii) filtering the aqueous pharmaceutical solution at a temperature of above 0° C. to 17.5° C. to produce a filtrate; and

(iii) filling a suitable container with the filtrate obtained after performing step (ii), so as to thereby prepare the pharmaceutical product comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

20. The process of claim 2, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

21. The process of claim 3, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

22. The process of claim 4, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

23. The process of claim 5, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

24. The process of claim 6, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

25. The process of claim 7, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

26. The process of claim 8, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

27. The process of claim 9, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

28. The process of claim 10, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

29. The process of claim 11, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

30. The process of claim 12, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

31. The process of claim 13, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

32. The process of claim 14, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

33. The process of claim 15, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

34. The process of claim 16, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

35. The process of claim 17, wherein the pharmaceutical preparation in the suitable container is an aqueous pharmaceutical solution comprising 40 mg/ml glatiramer acetate and 40 mg/ml mannitol.

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